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Mlostoń, Grzegorz ; Pieczonka, Adam M ; Ali, Korany A ; Linden, Anthony ; Heimgartner, Heinz

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## A new approach to morpholin-2-one derivatives via the reaction of $\beta$ -amino alcohols with dicyanofumarates

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**Dedicated to Prof. Rainer Beckert on the occasion of his 60th birthday**

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### Abstract

A novel approach for the synthesis of morpholin-2-one derivatives from dialkyl dicyanofumarates and  $\beta$ -amino alcohols is presented. The reaction takes place under mild conditions via an addition-elimination-lactonization pathway. The formation of the six-membered ring occurs selectively leading to a single diastereomer. In contrast to arylhydrazines, the reaction of hydrazine hydrate with dicyanofumarates yields pyrazol-3(2*H*)-ones and not 5-aminopyrazoles.

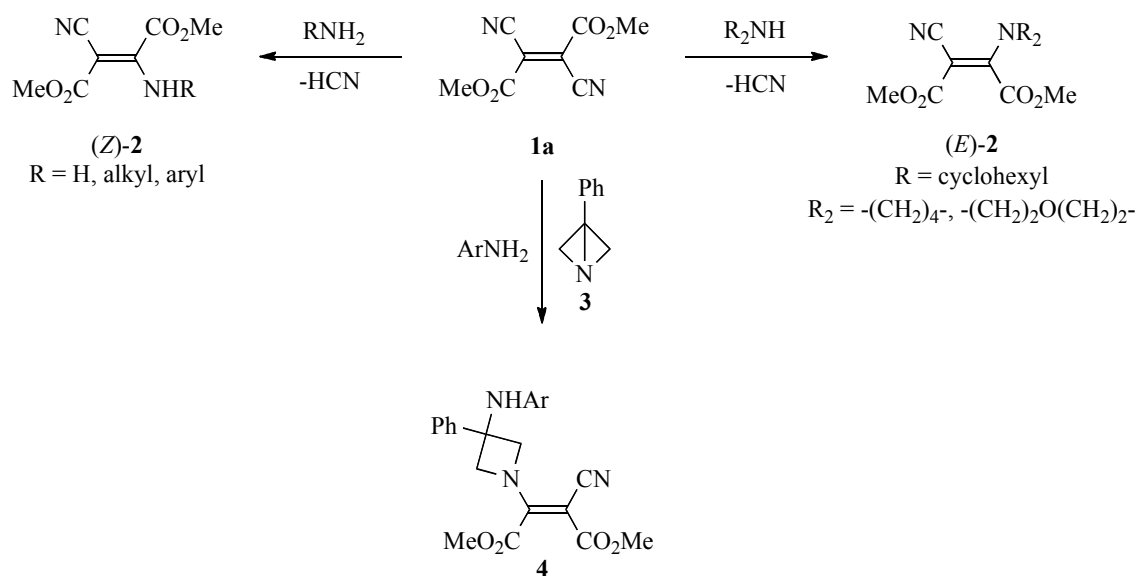
**Keywords:** Dicyanofumarates,  $\beta$ -amino alcohols, morpholin-2-ones, pyrazol-3-ones

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### Introduction

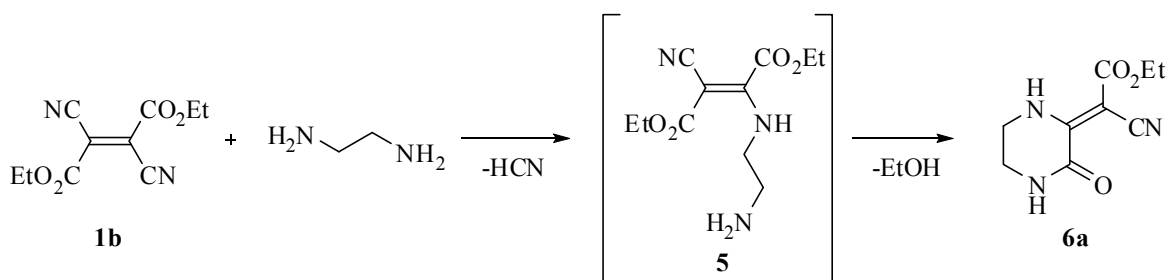
The electron-deficient dicyanofumarates **1** are known as excellent dienophiles,<sup>2</sup> dipolarophiles,<sup>3</sup> and Michael acceptors.<sup>4</sup> In the case of cycloaddition reactions, esters **1** as well as the stereoisomeric dicyanomaleates were used as a pair of substrates for the determination of the concertedness of these processes.<sup>2a,3a</sup> Reactions of dimethyl dicyanofumarate (**1a**) with ammonia, primary and secondary amines occur smoothly at room temperature according to the addition/elimination mechanism leading to 'push-pull' enamines of type **2** (Scheme 1).

Interestingly, enamines **2** are formed stereoselectively. Due to the strong hydrogen bond, the products obtained with ammonia and primary amines are (*Z*)-configured, whereas the (*E*)-configuration was determined for the products with secondary amines.<sup>4</sup> In attempted three-component reactions with dimethyl dicyanofumarate (**1a**), 3-phenyl-1-azabicyclo[1.1.0]butane (**3**) and a primary aliphatic amine, the only product obtained was the corresponding enamine (*Z*)-**2**.<sup>4c</sup> On the other hand, in experiments with less nucleophilic anilines or morpholine, the major products of type **4** were formed via the initial attack of **3** onto the C=C bond of **1a** and subsequent trapping of the intermediate azetidinium cation by the amine.<sup>4a,4c</sup>



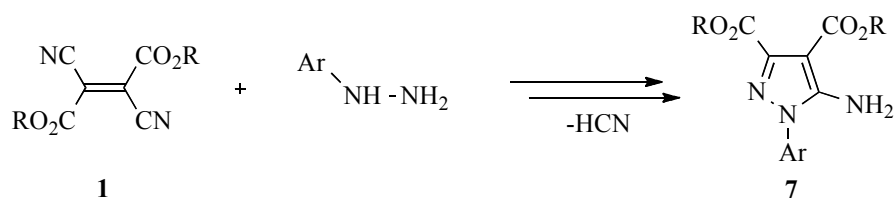
**Scheme 1.** Two- and three-component reactions of dimethyl dicyanofumarate (**1a**) with amines.<sup>4a,4c</sup>

Both ethylenediamine and *trans*-cyclohexane-1,2-diamine react with different dialkyl dicyanofumarates **1** yielding the corresponding piperazin-2-one derivatives of type **6**.<sup>5</sup> For example, diethyl dicyanofumarate (**1b**) and ethylenediamine react via the initiating step leading to enamine **5**, which has never been isolated and characterized. Under the reaction conditions, **5** undergoes spontaneous lactamization to give exclusively piperazin-2-one derivative **6a** (Scheme 2).<sup>5</sup>



**Scheme 2.** Reaction of diethyl dicyanofumarate (**1b**) with ethylenediamine.<sup>5</sup>

Another group of nitrogen di-nucleophiles used in reactions with **1** are arylhydrazines. The reactions in ethanol in the presence of sodium or ammonium acetate also occur stepwise leading to 5-aminopyrazole-3,4-dicarboxylates **7** (Scheme 3). Apparently, the initially formed enehydrazine intermediate undergoes a cyclization via nucleophilic attack onto the cyano group. The alternative lactamization was not observed.



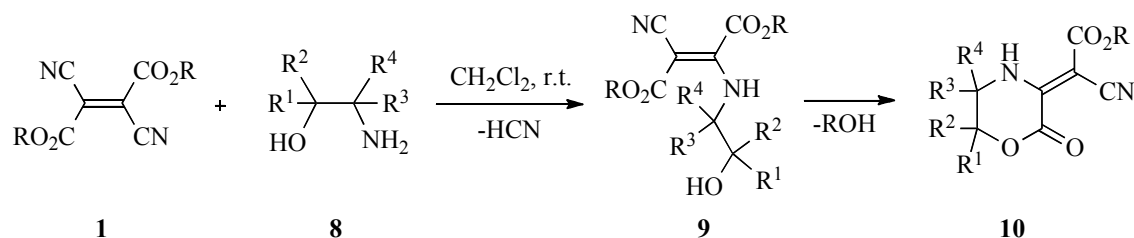
**Scheme 3.** Formation of 5-aminopyrazole-3,4-dicarboxylates from **1** and aryl hydrazines.<sup>6</sup>

To the best of our knowledge, reactions of **1** with other di-nucleophiles like  $\beta$ -amino alcohols or 1,2-diols, which potentially can lead to morpholine and 1,4-dioxane derivatives, respectively, have not been reported yet. The goal of the present study was the examination of the reaction of selected  $\beta$ -amino alcohols with dialkyl dicyanofumarates **1**.

## Results and Discussion

As an introductory experiment, diethyl dicyanofumarate (**1b**) was reacted with an equimolar amount of ethylenediamine in dichloromethane at room temperature with the aim of testing the reaction conditions.<sup>5</sup> The already described piperazinone **6a**<sup>5</sup> was isolated as the sole product in 51% yield. The structure is well confirmed by spectroscopic data. For example, in the <sup>1</sup>H-NMR spectrum, two broad NH absorptions are located at 7.39 and 10.18 ppm. The latter signal is attributed to the enamine NH group and correlates with earlier published data for a similar class of enamines.<sup>4b</sup> Two C=O absorptions appear at 1698 and 1659 cm<sup>-1</sup> in the IR spectrum (KBr) and at 169.1 and 157.8 ppm in the <sup>13</sup>C-NMR spectrum.

In an analogous experiment with **1a** and 2-aminoethanol (**8a**), the progress of the reaction was monitored by <sup>1</sup>H-NMR spectroscopy. In the spectrum registered after 30 min, only traces of both the starting material **1a** and the expected product **10a** could be detected. The major compound was characterized by two MeO absorptions at 3.98 and 3.79 ppm, indicative for the enamine intermediate **9a** (R = Me, R<sup>1</sup> – R<sup>4</sup> = H; cf. enamines of type (Z)-**2**<sup>4b</sup>). After 16 h, the lactonization of enamine **9a** was complete and morpholinone **10a** was isolated in 49% yield (Scheme 4, Table 1).



**Scheme 4.** Reactions of dicyanofumarates **1** with β-amino alcohols **8**.

Similar to the spectroscopic data of **6a**, the obtained product **10a** displays two C=O absorptions (IR: 1750 and 1678 cm<sup>-1</sup>, <sup>13</sup>C-NMR: 168.2 and 157.5 ppm). On the other hand, the <sup>1</sup>H-NMR spectrum reveals the presence of only one NH signal at 10.28 ppm. These data indicate that the exocyclic C=C bond is (*Z*)-configured in accordance with the spectroscopic data of structurally similar ‘push-pull’ enamines of type **2**.<sup>4b</sup>

The formation of the morpholinone derivative **10a** can be rationalized in analogy to the formation of **6a** (Scheme 2). The attack of the more nucleophilic NH<sub>2</sub> group of β-aminoethanol (**8a**) onto **1**, followed by elimination of HCN, leads to the proposed intermediate **9a** (Scheme 4). Then, the less nucleophilic OH group reacts selectively with the ‘geminal’ ester group yielding the six-membered lactone **10a** exclusively.

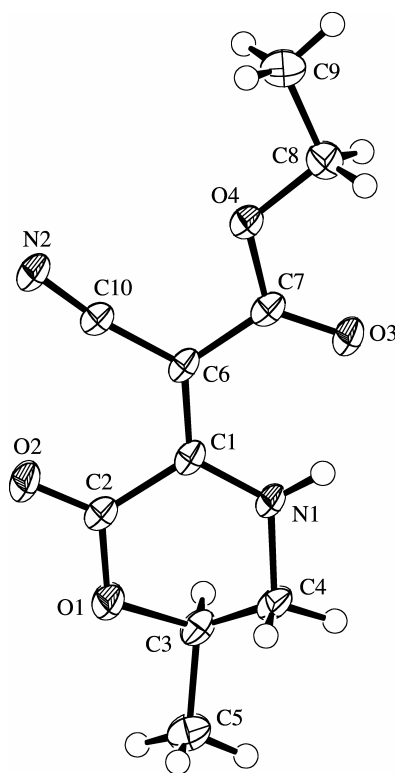
Based on the general protocol, a series of morpholinone derivatives **10a-10i** was prepared using differently substituted β-amino alcohols **8** and some dialkyl dicyanofumarates **1** (Table 1). In all cases, the reactions were performed in dichloromethane at room temperature, and the isolation of the products was achieved by fractional crystallization. Attempted chromatographic separations led to decomposition of the products. In all cases, only one product was obtained.

**Table 1.** Prepared morpholin-2-ones [(*Z*)-2-cyano-2-(2'-oxomorpholin-3'-ylidene)ethanoates **10a-10i**]

	<i>R</i>	<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup>	<i>R</i> <sup>4</sup>	Yield [%]	<i>mp</i> [°C]
<b>10a</b>	Me	H	H	H	H	49	274 – 276
<b>10b</b>	Me	Me	H	H	H	62	290 – 292
<b>10c</b>	Me	Ph	H	H	H	51	243 – 245
<b>10d</b>	Me	H	H	Me	Me	24	260 – 262
<b>10e</b>	Et	H	H	H	H	25	158 – 160
<b>10f</b>	Et	Me	H	H	H	80	234 – 236
<b>10g</b>	Et	Ph	H	H	H	62	268 – 270
<b>10h</b>	Et	H	H	Et	H	58	152 – 154
<b>10i</b>	iPr	Me	H	H	H	49	254 – 256 (decomp.)

In the case of **10f**, crystals suitable for an X-ray crystal structure determination were obtained, and the postulated (*Z*)-configuration of the exocyclic C=C bond was unambiguously confirmed (Figure 1).

The molecule is located on a crystallographic mirror plane, which results in disorder across the mirror plane of the methyl group and its adjacent C-atoms of the heterocyclic ring. The amine H-atom forms bifurcated hydrogen bonds, one arm of which is an intramolecular interaction with the ester carbonyl O-atom, while the other is an intermolecular interaction with the cyano N-atom of an adjacent molecule. The latter interaction links the molecules into extended chains which run parallel to the [100] direction and which can be described by a graph set motif<sup>8</sup> of C(6).



**Figure 1.** ORTEP plot<sup>7</sup> of the molecular structure of **10f** (arbitrary numbering of the atoms, 50% probability ellipsoids). The alternative conformation of the disordered ring is not shown.

In recent papers we described the preparation of 3-amino-1,1,1-trifluoro-2-arylpropan-2-ols.<sup>9</sup> Due to the importance of fluorinated systems, we decided to test the reaction of **1b** with 3-amino-1,1,1-trifluoro-2-phenylpropan-2-ol (**8**, R<sup>1</sup> = Ph, R<sup>2</sup> = CF<sub>3</sub>, R<sup>3</sup> = R<sup>4</sup> = H). Under standard conditions, the reaction stopped at the stage of the enamine **9j** (R<sup>1</sup> = Ph, R<sup>2</sup> = CF<sub>3</sub>, R<sup>3</sup> = R<sup>4</sup> = H), and no lactonization occurred after heating of the reaction mixture. Even after replacement of dichloromethane by 1,2-dichloroethane or ethanol and heating to reflux for several hours, no morpholinone was obtained. We propose that the reduced nucleophilicity of the OH group in **9j**



## Conclusions

The results described in this paper show that dialkyl dicyanofumarates **1** can be used as building blocks for the preparation of functionalized morpholin-2-ones **10** upon treatment with  $\beta$ -amino alcohols. This new method extends known protocols for the synthesis of morpholine derivatives. Taking into account that both dicyanofumarates and  $\beta$ -amino alcohols are easily available starting materials, this method can be applied successfully for the regioselective synthesis of a variety of morpholin-2-one derivatives. The importance of morpholinones and other morpholine derivatives as biologically relevant substances is well documented.<sup>11</sup> Unexpectedly, the reactions of dicyanofumarates with hydrazine hydrate lead to pyrazolones and not to aminopyrazoles, as reported for the reactions with arylhydrazines. Whereas in the case of the reaction with hydrazine an ester group is involved in the cyclization, it is the cyano group in the case of arylhydrazines.

## Experimental Section

**General.** Melting points were determined in a capillary using a Melt-Temp. II apparatus (Aldrich) or STUART SMP30 and are uncorrected. The IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions ( $\nu$ ) in  $\text{cm}^{-1}$ . The  $^1\text{H}$ - (600 MHz),  $^{13}\text{C}\{^1\text{H}\}$ - (150 MHz) and  $^{19}\text{F}$ -NMR (565 MHz) spectra were measured on a Bruker Avance III instrument using solvent signals as reference. Chemical shifts ( $\delta$ ) are given in ppm and coupling constants  $J$  in Hz. Assignments of signals in  $^{13}\text{C}$ -NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker Esquire LC spectrometers. All solvents are commercially available reagents and used as received. Dimethyl-, diethyl- and diisopropyl dicyanofumarates **1a-1c** were prepared from corresponding cyanoacetates by treatment with pure thionyl chloride according to the published general procedure.<sup>12</sup> *Attention:* reaction could be performed successfully only when the commercial thionyl chloride was purified by distillation over quinoline and linseed oil following the recommended procedure.<sup>13</sup>

### Reactions of $\beta$ -amino alcohols **8** or hydrazine hydrate with dicyanofumarates **1**

To a solution of  $\beta$ -amino alcohol **8** or hydrazine hydrate (1 mmol) in  $\text{CH}_2\text{Cl}_2$  or EtOH (1 mL), respectively, 1 mmol of dicyanofumarate **1** was added at 0 °C. The mixture was stirred for 0.5 to 16 h at room temperature, the solvent was evaporated under vacuum, and the residue was treated with methanol, filtered, and crystallized from methanol. Product **9i** was purified by chromatography (PLC plates,  $\text{SiO}_2$ , AcOEt:petroleum ether 3:7).

**Ethyl (Z)-2-cyano-2-(3'-oxopiperazin-2'-ylidene)ethanoate (6a).**<sup>5</sup> Reaction time 0.5 h, colorless solid, yield 51%, 0.106 g, mp 191–193 °C (MeOH), mp 187–188.5 (EtOH). IR: 3323m (br., NH), 3292m (br., NH), 3221m (br.), 2207m ( $\text{C}\equiv\text{N}$ ), 1698m ( $\text{C}=\text{O}$ ), 1659m ( $\text{C}=\text{O}$ ), 1599m, 1251m.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 10.18, 7.39 (2 br. s, 2 NH); 4.29 (q,  $J = 7.1$ ,  $\text{MeCH}_2\text{O}$ ); 3.65–3.58 (m,



2 CH<sub>2</sub>); 1.37 (*t*, *J* = 7.1, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 169.1, 157.8 (2 C=O); 156.1, 73.6 (C=C); 116.7 (C≡N); 61.4 (MeCH<sub>2</sub>O); 39.9, 39.5 (2 CH<sub>2</sub>); 14.2 (MeCH<sub>2</sub>O).

**Diethyl (Z)-2-cyano-3-[(3',3',3'-trifluoro-2'-hydroxy-2'-phenylpropyl)amino]fumarate (9j).** Reaction time 16 h, yellow oil, yield 83%, 0.167 g. IR: 3335s (NH), 2986m, 2217s (C≡N), 1744vs (C=O), 1674vs (C=O), 1370m, 1028m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.52 (br. *s*, NH); 7.55–7.41 (*m*, 5 arom. H); 4.49–4.30, 4.18–4.15, 3.96–3.89 (3 *m*, 3 CH<sub>2</sub>); 1.42 (*t*, *J* = 7.1, MeCH<sub>2</sub>O); 1.26 (*t*, *J* = 7.1, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 167.5, 161.7 (2 C=O); 160.6, 73.9 (C=C); 134.1, 129.5, 129.0, 126.0 (6 arom. C); 115.8 (C≡N); 64.5, 61.5, 50.3 (3 CH<sub>2</sub>); 14.1, 13.6 (2 Me). HR-ESI-MS: found 401.1314 (for [M+H]<sup>+</sup>, C<sub>18</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>), Calcd 401.1319; found 423.1136 (for [M+Na]<sup>+</sup>, C<sub>18</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>5</sub>), Calcd 423.1138.

**Methyl (Z)-2-cyano-2-(2'-oxomorpholin-3'-ylidene)ethanoate (10a).** Reaction time 16 h, colorless solid, yield 49%, 0.096 g, mp 274–276 °C (MeOH). IR: 3215m (NH), 3174m, 2210s (C≡N), 1750vs (C=O), 1678vs (C=O), 1605vs, 1282m, 1260m, 999m, 777m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 10.28 (br. *s*, NH); 4.56–4.53 (*m*, OCH<sub>2</sub>); 3.73 (*s*, OMe); 3.65–3.63 (*m*, NCH<sub>2</sub>). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.2, 157.5 (2 C=O); 152.9, 72.3 (C=C); 117.1 (C≡N); 67.3 (OCH<sub>2</sub>); 52.3 (OMe); 39.8 (NCH<sub>2</sub>). HR-ESI-MS: found 197.0556 (for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>9</sub>N<sub>2</sub>O<sub>4</sub>), Calcd 197.0557.

**Methyl (Z)-2-cyano-2-(6'-methyl-2'-oxomorpholin-3'-ylidene)ethanoate (10b).** Reaction time 16 h, colorless solid, yield 62%, 0.13 g, mp 290–292 °C (MeOH). IR: 3233m (NH), 3184m, 2211s (C≡N), 1739vs (C=O), 1685vs (C=O), 1605vs, 1291m, 1270m, 1258m, 778m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 10.25 (br. *s*, NH); 4.88–4.85 (*m*, CH); 3.73 (*s*, OMe); 3.72–3.68, 3.39–3.34 (2 *m*, CH<sub>2</sub>); 1.31 (*d*, *J* = 5.9, Me). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.1, 157.6 (2 C=O); 152.4, 72.3 (C=C); 117.0 (C≡N); 75.0 (CH); 52.3 (OMe); 45.0 (CH<sub>2</sub>); 17.6 (Me). HR-ESI-MS: found 211.0711 (for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>), Calcd 211.0713.

**Methyl (Z)-2-cyano-2-(2'-oxo-6'-phenylmorpholin-3'-ylidene)ethanoate (10c).** Reaction time 16 h, colorless solid, yield 51%, 0.14 g, mp 243–245 °C (MeOH). IR: 3234s (NH), 2208s (C≡N), 1746vs (C=O), 1681vs (C=O), 1606vs, 1273m, 1203m, 693m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 10.36 (br. *s*, NH); 7.47–7.44 (5 arom. H); 5.89–5.87 (*m*, CH); 3.87–3.80 (*m*, CH<sub>2</sub>); 3.75 (*s*, OMe). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.1, 157.6 (2 C=O); 152.4, 72.6 (C=C); 129.8, 129.2, 128.8, 127.3 (6 arom. C); 117.0 (C≡N); 79.1 (CH); 52.4 (OMe); 45.1 (CH<sub>2</sub>). HR-ESI-MS: found 295.0687 (for [M+Na]<sup>+</sup>, C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 295.0689.

**Methyl (Z)-2-cyano-2-(5',5'-dimethyl-2'-oxomorpholin-3'-ylidene)ethanoate (10d).** Reaction time 16 h, colorless solid, yield 24%, 0.054 g, mp 260–262 °C (MeOH). IR: 3150m, 2212s (C≡N), 1756vs (C=O), 1682vs (C=O), 1606vs, 1293m, 1273m, 1174m, 991m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 10.08 (br. *s*, NH); 4.43 (*s*, CH<sub>2</sub>); 3.74 (*s*, OMe); 1.35 (*s*, 2 Me). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.5, 157.3 (2 C=O); 151.3, 72.7 (C=C); 116.6 (C≡N); 74.7 (CH<sub>2</sub>); 52.5 (OMe); 51.4 (C(5')); 24.1 (2 Me). HR-ESI-MS: found 247.0687 (for [M+Na]<sup>+</sup>, C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 247.0689.

**Ethyl (Z)-2-cyano-2-(2'-oxomorpholin-3'-ylidene)ethanoate (10e).** Reaction time 16 h, colorless solid, yield 25%, 0.053 g, mp 158–160 °C (MeOH). IR: 3224m (NH), 3183m, 2208s

(C≡N), 1752vs (C=O), 1671vs (C=O), 1605vs, 1284m, 1260m, 1184m, 1011m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.20 (br. *s*, NH); 4.57–4.55 (*m*, OCH<sub>2</sub>); 4.29 (*q*, *J* = 7.0, MeCH<sub>2</sub>O); 3.67–3.65 (*m*, NCH<sub>2</sub>); 1.35 (*t*, *J* = 7.0, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 168.4, 156.1 (2 C=O); 151.4 (C(3')); 115.3 (C≡N); 66.7 (OCH<sub>2</sub>); 61.9 (MeCH<sub>2</sub>O); 39.4 (NCH<sub>2</sub>); 14.2 (MeCH<sub>2</sub>O); (C(2) hidden under CDCl<sub>3</sub> signal). HR-ESI-MS: found 233.0532 (for [M+Na]<sup>+</sup>, C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 233.0533.

**Ethyl (Z)-2-cyano-2-(6'-methyl-2'-oxomorpholin-3'-ylidene)ethanoate (10f).** Reaction time 16 h, colorless solid, yield 80%, 0.180 g, mp 234–236 °C (MeOH). IR: 3235m (NH), 2981m, 2210s (C≡N), 1745vs (C=O), 1678vs (C=O), 1609vs, 1280m, 1091m, 777m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.16 (br. *s*, NH); 4.75–4.73 (*m*, CH); 4.28 (*q*, *J* = 7.0, MeCH<sub>2</sub>O); 3.58–3.56, 3.42–3.37 (2*m*, CH<sub>2</sub>); 1.49 (*d*, *J* = 6.5, Me); 1.35 (*t*, *J* = 7.0, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 168.4, 156.5 (2 C=O); 151.0 (C(3')); 115.4 (C≡N); 74.7 (CH); 61.8 (MeCH<sub>2</sub>O); 44.9 (CH<sub>2</sub>); 17.7 (Me); 14.2 (MeCH<sub>2</sub>O); (C(2) hidden under CDCl<sub>3</sub> signal). HR-ESI-MS: found 225.0867 (for [M+H]<sup>+</sup>, C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>), Calcd 225.0870.

**Ethyl (Z)-2-cyano-2-(2'-oxo-6'-phenylmorpholin-3'-ylidene)ethanoate (10g).** Reaction time 16 h, colorless solid, yield 62%, 0.177 g, mp 268–270 °C (MeOH). IR: 3236m (NH), 2207s (C≡N), 1749vs (C=O), 1677vs (C=O), 1614vs, 1286m, 1279m, 698m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.26 (br. *s*, NH); 7.46–7.39 (5 arom. H); 5.62–5.60 (*m*, CH); 4.30 (*q*, *J* = 7.0, MeCH<sub>2</sub>O); 3.78–3.67 (*m*, CH<sub>2</sub>); 1.36 (*t*, *J* = 7.0, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 168.4, 156.5 (2 C=O); 151.0 (C(3')); 133.7, 129.9, 129.2, 126.2 (6 arom. C); 115.3 (C≡N); 79.4 (CH); 61.9 (MeCH<sub>2</sub>O); 45.5 (CH<sub>2</sub>); 14.2 (MeCH<sub>2</sub>O); (C(2) hidden under CDCl<sub>3</sub> signal). HR-ESI-MS: found 309.0846 (for [M+Na]<sup>+</sup>, C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 309.0846.

**Ethyl (Z)-2-cyano-2-(5'-ethyl-2'-oxomorpholin-3'-ylidene)ethanoate (10h).** Reaction time 16 h, colorless solid, yield 58%, 0.137 g, mp 152–154 °C (MeOH). IR: 3235m (NH), 2967m, 2211s (C≡N), 1750vs (C=O), 1679vs (C=O), 1600vs, 1286m, 1261m, 1186m, 769m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.26 (br. *s*, NH); 4.51–4.49 (*m*, 1H OCH<sub>2</sub>); 4.30–4.26 (*m*, 1H OCH<sub>2</sub>, MeCH<sub>2</sub>O); 3.67–3.64 (*m*, CH); 1.74–1.68 (*m*, CH<sub>2</sub>); 1.36 (*t*, *J* = 7.0, MeCH<sub>2</sub>O); 1.10 (*t*, *J* = 7.6, Me). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 168.5, 156.2 (2 C=O); 150.8, 76.3 (C=C); 115.3 (C≡N); 70.1 (CH<sub>2</sub>); 61.8 (MeCH<sub>2</sub>O); 50.9 (CH); 24.2 (CH<sub>2</sub>); 14.2 (MeCH<sub>2</sub>O); 9.8 (Me). HR-ESI-MS: found 261.0848 (for [M+Na]<sup>+</sup>, C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 261.0846.

**Isopropyl (Z)-2-cyano-2-(6'-methyl-2'-oxomorpholin-3'-ylidene)ethanoate (10i).** Reaction time 16 h, colorless solid, yield 49%, 0.117 g, mp 254–256 °C (decomp.) (MeOH). IR: 3240m (NH), 2980m, 2209s (C≡N), 1744vs (C=O), 1671vs (C=O), 1611vs, 1289m, 1116m, 774m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.18 (br. *s*, NH); 5.11–5.06 (*m*, CH); 4.76–4.72 (*m*, Me<sub>2</sub>CHO); 3.59–3.55, 3.41–3.36 (2*m*, CH<sub>2</sub>); 1.49 (*d*, *J* = 6.5, Me); 1.34–1.32 (*m*, Me<sub>2</sub>CHO). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 168.0, 156.5 (2 C=O); 150.5, 76.9 (C=C); 115.3 (C≡N); 74.6 (CH); 69.9 (Me<sub>2</sub>CHO); 44.9 (CH<sub>2</sub>); 21.7, 21.7 (Me<sub>2</sub>CHO); 17.8 (Me). HR-ESI-MS: found 261.0844 (for [M+Na]<sup>+</sup>, C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Na), Calcd 261.0846.

**Diisopropyl (Z)-2-cyano-3-hydrazinobut-2-enedioate (11c).** Reaction time 16 h, colorless solid, yield 82%, 0.160 g, mp 184–186 °C (EtOH). IR: 3326s (NH), 3269m, 2979m, 1710vs (C=O), 1626s, 1522m, 1303m, 1098m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 12.13 (br. *s*, NH); 6.08 (br. *s*,

NH<sub>2</sub>); 5.05–4.98 (*m*, Me<sub>2</sub>CHO); 1.27, 1.21 (2 *d*, *J* = 6.0, 6.6 resp., 2 Me<sub>2</sub>CHO). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 163.2, 162.6 (2 C=O); 151.7 (C≡N); 144.3 (C(3)); 91.9 (C(2)); 68.4, 66.4 (2 Me<sub>2</sub>CHO); 21.9, 21.6 (2 Me<sub>2</sub>CHO). HR-ESI-MS: found 256.1289 (for [M+H]<sup>+</sup>, C<sub>11</sub>H<sub>18</sub>N<sub>3</sub>O<sub>4</sub>), Calcd 256.1292; found 278.1111 (for [M+Na]<sup>+</sup>, C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>4</sub>), Calcd 278.1111.

**Methyl 4-cyano-5-oxo-1,2-dihydropyrazole-3-carboxylate (12a).** Reaction time 20 min, yellow solid, yield 60%, 0.100 g, mp 196–198 °C (*i*PrOH). IR: 3325s (NH), 2966m (br.), 2216s (C≡N), 1713s (C=O), 1607m, 1488m, 1134m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 7.18 (br. *s*, NH); 3.70 (*s*, Me). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.4, 162.2 (2 C=O); 140.2 (C(3)); 119.0 (C≡N); 69.4 (C(4)); 51.2 (Me). HR-ESI-MS: found 190.0223 (for [M+Na]<sup>+</sup>, C<sub>6</sub>H<sub>5</sub>N<sub>3</sub>NaO<sub>3</sub>), Calcd 190.0223.

**Ethyl 4-cyano-5-oxo-1,2-dihydropyrazole-3-carboxylate (12b).** Reaction time 20 min, reddish solid, yield 67%, 0.121 g, mp 214–216 °C (EtOH). IR: 3358s (NH), 2984m (br.), 2206s (C≡N), 1715s (C=O), 1604s, 1482m, 1247m, 1132m. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 7.16 (br. *s*, NH); 4.19 (*q*, *J* = 7.2, MeCH<sub>2</sub>O); 1.24 (*t*, *J* = 7.2, MeCH<sub>2</sub>O). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 168.3, 161.7 (2 C=O); 140.4 (C(3)); 119.4 (C≡N); 69.6 (C(4)); 59.7 (MeCH<sub>2</sub>O); 14.3 (MeCH<sub>2</sub>O). HR-ESI-MS: found 204.0378 (for [M+Na]<sup>+</sup>, C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>NaO<sub>3</sub>), Calcd 204.0380.

### X-Ray Crystal Structure Determination of 10f

All measurements were made on an *Oxford Diffraction SuperNova* area-detector diffractometer<sup>14</sup> using MoK<sub>α</sub> radiation ( $\lambda = 0.71073$  Å) and an *Oxford Instruments Cryojet XL* cooler. Data reduction was performed with *CrysAlisPro*.<sup>14</sup> The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method<sup>14</sup> was applied. The space group was determined from the systematic absences, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections were merged. The data collection and refinement parameters are given below. A view of the molecule is shown in the *Figure*. The structure was solved by direct methods using *SHELXS97*,<sup>15</sup> which revealed the positions of all non-hydrogen atoms. The molecule is located on a crystallographic mirror plane, which results in equal occupancy disorder across the mirror plane of the methyl group and its adjacent C-atoms of the heterocyclic ring. The non-hydrogen atoms were refined anisotropically. The amine H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. This H-atom is also disordered across the mirror plane. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U<sub>eq</sub> of its parent C-atom (1.5U<sub>eq</sub> for the methyl group). The refinement of the structure was carried out on *F*<sup>2</sup> by using full-matrix least-squares procedures, which minimized the function  $\sum w(F_o^2 - F_c^2)^2$ . A correction for secondary extinction was applied. Neutral atom scattering factors for non-hydrogen atoms were taken from ref.<sup>16a</sup>, and the scattering factors for hydrogen atoms were taken from ref.<sup>17</sup>. Anomalous dispersion effects were included in *F*<sub>c</sub> (ref.<sup>18</sup>); the values for *f*' and *f*'' were those of ref.<sup>16b</sup>. The values of the mass

attenuation coefficients are those of ref.<sup>16c</sup>. The *SHELXL97* program<sup>19</sup> was used for all calculations.

Crystallographic data for compound **10f**.<sup>20</sup> Crystallized from MeOH/CH<sub>2</sub>Cl<sub>2</sub>, C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>; *M* = 224.21 g mol<sup>-1</sup>; colorless, prism; crystal dimensions: 0.10 × 0.20 × 0.22 mm; monoclinic; space group: *P*2<sub>1</sub>/*m*; *Z* = 2; *a* = 7.3528(2) Å, *b* = 6.4747(3) Å, *c* = 11.3185(4) Å, *β* = 90.645(3)°, *V* = 538.81(3) Å<sup>3</sup>; *T* = 160 K; *D<sub>x</sub>* = 1.382 g cm<sup>-3</sup>; *μ*(MoK<sub>α</sub>) = 0.108 mm<sup>-1</sup>; scan type: *ω*, 2*θ*(max) = 56.6°; total reflections measured: 4675; symmetry independent reflections: 1295; reflections with *I* > 2 $\sigma$ (*I*): 1051; reflections used in refinement: 1295; parameters refined: 111; final *R*(*F*) [*I* > 2 $\sigma$ (*I*) reflections]: 0.0418; *wR*(*F*<sup>2</sup>) (all data): 0.1124; weights: *w* = [ $\sigma^2(F_o^2) + (0.0478P)^2 + 0.1532P$ ]<sup>-1</sup> where *P* = (*F<sub>o</sub>*<sup>2</sup> + 2*F<sub>c</sub>*<sup>2</sup>)/3; goodness of fit: 1.077; final  $\Delta_{\text{max}}/\sigma$  = 0.001;  $\Delta\rho$  (max; min) = 0.30; -0.20 [e Å<sup>-3</sup>].

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